



TITLE:

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# Effect on Treadmill Exercise Capacity, Myocardial Ischemia, and Left Ventricular Function as a Result of Repeated Whole-Body Periodic Acceleration With Heparin Pretreatment in Patients With Angina Pectoris and Mild Left Ventricular Dysfunction

Running title: Periodic Acceleration for Angina

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References 30, tables 2 and figures 3.

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## Abstract

Whole-body periodic acceleration (WBPA) has been developed as a passive exercise device capable of improving endothelial function by applying pulsatile shear stress to vascular endothelium. We hypothesized that treatment with WBPA improves exercise capacity, myocardial ischemia and left ventricular (LV) function as a result of increased coronary and peripheral vasodilatory reserves in angina patients. Twenty-six angina patients who were not indicated for percutaneous coronary intervention and/or coronary artery bypass grafting were randomly assigned to remain sedentary (Sedentary group) or to undergo 20 sessions of WBPA with the motion platform for 4 weeks (WBPA group) in addition to conventional medical treatment. WBPA was applied at 2 to 3 Hz and approximately  $\pm 2.2 \text{ m/sec}^2$  for 45 min. We repeated the symptom-limited treadmill exercise test and adenosine sestamibi myocardial scintigraphy. In the WBPA group, the exercise time until 0.1 mV ST depression increased by 53% ( $p < .01$ ), and the double product at 0.1 mV ST depression by 23% ( $p < .001$ ). The severity score of myocardial scintigraphy during adenosine infusion decreased from  $20 \pm 10$  to  $14 \pm 8$  ( $p < .001$ ), and resting severity score also decreased from  $13 \pm 10$  to  $8 \pm 10$  ( $p < .01$ ). In resting scintigraphic images, LV end-diastolic volume index decreased by 18% ( $p < .01$ ) with an augmentation of LV ejection fraction from  $50 \pm 16\%$  to  $55 \pm 16\%$  ( $p < .01$ ). In contrast, all aforementioned parameters remained unchanged in the sedentary group. In conclusion, treatment with WBPA for angina patients ameliorates exercise capacity, myocardial ischemia and LV function.

**Key words:** Heparin · Myocardial scintigraphy · Passive exercise · Treadmill exercise test

## Introduction

Recently, Sackner et al.<sup>1, 2</sup> invented whole-body periodic acceleration (WBPA), a new therapeutic device capable of improving endothelial function by applying pulsatile shear stress to vascular endothelium, presumably owing to the production and release of vasoactive substances such as nitric oxide.<sup>3, 4</sup> Heparin possesses several functions besides an anticoagulant effect. Heparin potentiates and accelerates coronary collateral growth resulting from interaction with angiogenic growth factors.<sup>5</sup> Heparin also increases the bioavailability of nitric oxide by liberating vessel-immobilized myeloperoxidase.<sup>6</sup> We designed the present study to test the impact of repeated WBPA therapy with heparin pretreatment on exercise capacity, myocardial ischemia, and left ventricular (LV) function in patients with angina pectoris and mild LV dysfunction.

## Methods

We investigated 26 patients (19 men, 7 women) aged between 45 and 86 years (mean  $68 \pm 10$  years) with chronic effort angina and mild LV dysfunction with an ejection fraction (EF) below 55% (mean  $51 \pm 10$  %). All had angiographically proven significant coronary narrowing ( $\geq 75\%$ ) involving one or more major coronary arteries and developed  $\geq 0.1$  mV ST-segment depression during treadmill exercise testing. None had acute exacerbation of symptoms in the preceding 6 months. Patients were randomized to remain sedentary (Sedentary group,  $n = 13$ ) or to undergo heparin WBPA therapy (WBPA group,  $n = 13$ ). All patients underwent conventional medical therapy throughout the study. WBPA was applied

with a gurney-like motion platform device (Acceleration Therapeutics AT101; Non-Invasive Monitoring Systems; North Bay Village, FL) at a frequency of 2-3 Hz and approximately  $\pm 2.2 \text{ m/sec}^2$  for 45 minutes.<sup>1,2</sup> A single intravenous dose of heparin (5,000 IU) was given 10 to 20 min before each WBPA. The procedure was repeated 20 times over 4 weeks. Primary endpoints of the present study were improvements in exercise capacity, myocardial ischemia and LV size and function. The study protocol complied with the Declaration of Helsinki was approved by the ethics committee of Kitano Hospital, and all patients gave written informed consent for the study.

Before performing the baseline exercise test, all patients carried out preliminary treadmill exercise several times to habituate themselves to the test. All anti-angina medications were withdrawn at least 2 days before the study. Sublingual nitroglycerin was allowed for angina symptom relief. Symptom-limited graded treadmill exercise testing was performed with a standard Bruce protocol in a fasting state, and a post-treatment treadmill exercise test was repeated at the same time of day as the baseline test.<sup>7</sup> A 12-lead electrocardiogram was recorded at rest and 1-minute intervals until the onset of limiting chest pain, leg fatigue or  $\geq 0.2 \text{ mV}$  ST-segment depression. Blood pressure was measured with a sphygmomanometer during each minute of exercise and recovery. Time to 0.1 mV ST-segment depression was defined as the elapsed time from initiation of exercise to the occurrence of horizontal or down-sloping 0.1-mV ST-segment depression measured at 80 ms after the J point. In this study, the heart rate and systolic blood pressure at the onset of 0.1 mV ST-segment depression

were measured to determine the ischemic threshold. All exercise tests and ST-segment evaluations were performed by investigators blinded to the results of coronary angiograms and treatment status.

Adenosine myocardial perfusion single photon emission computed tomography was performed as described previously.<sup>8</sup> Adenosine was infused at 140  $\mu\text{g/kg/min}$  for 5 minutes. At the end of the second minute, Tc-99m sestamibi (25-40 mCi) was injected, and myocardial perfusion single photon emission computed tomography acquisition was started approximately 60 minutes later. We used software developed at Cedars-Sinai Medical Center, called quantitative gated single photon emission computed tomography,<sup>9, 10</sup> capable of providing simultaneous assessment of LV perfusion, global function (either systolic and diastolic) and regional wall thickening and motion. Visual interpretation of myocardial perfusion single photon emission computed tomography images was based on short-axis and vertical long-axis tomograms divided into 17 segments.<sup>11</sup> Each segment was scored by 2 expert observers blinded to the treatment group using a 5-point scoring system (0, normal; 1, mildly abnormal; 2, moderately abnormal; 3, severely abnormal; and 4, absence of segmental uptake). Subsequently, summed stress and rest scores were calculated by summing of respective segmental scores.<sup>12</sup> The maximal score was therefore 68 (17 segments  $\times$  score 4). When visual scoring was different between the 2 observers, they assessed again the myocardial perfusion images and reached a consensus. Quantitative measurements of LVEF using gated perfusion single photon emission computed tomography were usually

volume-based rather than count-based methods. In particular, the time-volume curve derived from 16-frame gating allowed the end-diastolic volume (EDV) and end-systolic volume (ESV) of the LV cavity to be identified, from which the LVEF was calculated as follows:  $\%LVEF = (LVEDV - LVESV) / LVEDV \times 100$ .

Data are expressed as the mean  $\pm$  SD. A two-way analysis of variance using Bonferroni's method was carried out to investigate differences in the treadmill exercise test and adenosine myocardial perfusion scintigraphy. Significance was designated at the probability value of  $p < 0.05$ .

## Results

All 26 patients completed the protocol without any complications or adverse effects. No hemorrhagic tendency was noted in any of the patients treated with heparin. Weekly urinalysis and stool occult blood tests revealed negative results.

The baseline characteristics of the study patients are listed in Table 1. There were no significant differences in age, gender, risk factors and disease complications between the 2 groups. The distribution of the ischemia-related artery was similar in the 2 groups. The number of involved vessels was also comparable between the 2 groups. Similarly, there were no significant differences in medication between the 2 groups.

Exercise time and hemodynamic parameters at rest and at 0.1 mV ST depression during the treadmill exercise test are summarized in Table 2. There were no significant differences in resting hemodynamic parameters at baseline and after treatment between the 2 groups. In

the sedentary group, the exercise time to 0.1 mV ST depression remained unchanged before and after the conventional treatment. In contrast, in the WBPA group, WBPA with heparin pretreatment significantly increased the exercise time to 0.1 mV ST depression. In the sedentary group, the double product at 0.1 mV ST depression remained unchanged before and after conventional treatment. In contrast, in the WBPA group it was significantly ( $p < .001$ ) increased.

Figure 1 shows 2 representative cases in each group. In a patient of the sedentary group, in the LV short-axial and horizontal long-axial view, posterolateral hypoperfusion or defect and LV size remained unchanged as determined by both stress and at rest imaging after conventional treatment (Figure 1; left panels). In a patient of the WBPA group, in the LV short-axial and horizontal long-axial view, posterolateral hypoperfusion or defect clearly improved as determined by both stress and at rest imaging after heparin WBPA treatment. In addition, LV size remarkably decreased as determined by both stress and at rest imaging after treatment (Figure 1; right panels). At baseline, the summed stress and rest scores of adenosine myocardial perfusion scintigrams were comparable between the 2 groups. The summed stress and rest scores remained unchanged in the sedentary group. In contrast, in the WBPA group after treatment with heparin WBPA therapy, the summed stress and rest scores significantly decreased (Figure 2). Changes in global LV parameters (EDVI, ESVI, EF) are summarized in Figure 3. At baseline, the LVEDVI, LVESVI and LVEF were similar between the 2 groups. In the sedentary group, all global LV parameters remained unchanged



after conventional treatment (Figure 3; left panels). In the WBPA group, we found significantly smaller LVEDVI and LVESVI after treatment. In addition, LVEF significantly increased (Figure 3; right panels).

## Discussion

The present study has demonstrated that repeated WBPA with a motion platform combined with heparin pretreatment attenuates stress-induced myocardial ischemia and improves resting LV systolic function with a reversal of LV remodeling in patients with angina pectoris and mild LV dysfunction. This is the first clinical report to show that heparin WBPA treatment is effective in alleviating exercise-induced myocardial ischemia and improving cardiac morphology and performance in patients with advanced coronary artery disease.

In our treated patients, the rate-pressure product at 0.1 mV ST depression increased by 23% with heparin WBPA treatment. This implies an increase in blood flow supply to the potentially ischemic area,<sup>7, 13, 14</sup> which was confirmed by myocardial perfusion scintigraphy during adenosine infusion. These findings suggest that coronary flow reserve to the potentially ischemic area was augmented by the treatment. There are 3 possible mechanisms of the increased flow reserve. First, increased pulsatile shear stress resulting from WBPA treatment activates production and release of angiogenic growth factors and leads to arteriogenesis.<sup>5, 15</sup> Second, WBPA increases the release from the endothelium of vasodilatory molecules such as nitric oxide, adrenomedullin, prostacyclin, and others.<sup>3</sup>

These substances may contribute to arteriogenesis and/or angiogenesis.<sup>16, 17</sup> Third, endothelial dysfunction plays an important role in the pathogenesis of decreased coronary flow reserve.<sup>18</sup> Improvement of coronary endothelial function, which is speculated from the improved endothelial function in the peripheral circulation with WBPA,<sup>19, 20</sup> enhances coronary flow reserve in the area supplied with severely narrowed coronary artery and/or collateral vessels.<sup>21</sup> Indeed, we have recently documented that WBPA improves coronary flow reserve in healthy subjects and patients with coronary artery disease.<sup>22</sup>

In our treated patients, the rate-pressure product at the same exercise time was significantly decreased (data not shown). This implies that heparin WBPA treatment may provide a peripheral effect via nitric oxide production, which is the case in exercise rehabilitation in patients with coronary artery disease.<sup>23</sup> Thus, the increased exercise capacity after the treatment may, at least in part, be attributed to a training effect. Alternatively, cardiac protection may have been achieved as a result of WBPA. WBPA has also been shown to upregulate eNOS in the heart.<sup>4</sup> Cardiac preconditioning is a polygenic process resulting in de novo synthesis of cardioprotective proteins.<sup>24</sup> The preconditioning-mimetic actions of nitroglycerin have been demonstrated in an elegant study by Leeser et al..<sup>25</sup> The preconditioning effect of WBPA was also documented in an animal study.<sup>26</sup> Thus, cardiac preconditioning potentially suppresses myocardial oxygen consumption during exercise with a resultant improvement of exercise capacity.

In our patients with heparin WBPA treatment, scintigraphically evaluated resting LV

function significantly improved. It is well known that “hibernating” myocardium recovers contractile force soon after revascularization procedures such as percutaneous coronary intervention and coronary artery bypass grafting.<sup>27</sup> A reduction in “hibernating” myocardium in our treated patients was shown by the fact that the defect score of myocardial perfusion scintigraphy at rest was significantly decreased after treatment. Another explanation of LV functional recovery is an unloading effect resulting from decreased peripheral vascular resistance as a result of improved endothelial function in peripheral circulation.

Heparin was administered as a pretreatment of WBPA for two reasons. First, we have previously developed heparin exercise treatment for patients with chronic effort angina.<sup>13</sup> The efficacy of heparin on coronary collateral growth has been confirmed by several clinical studies.<sup>5</sup> It is important that heparin does not initiate but rather potentiates arteriogenesis in combination with exercise. Therefore, the presence of angiogenic growth factors is indispensable for the effect of heparin. Indeed, in angina patients treated with heparin alone the total treadmill exercise time remained unchanged ( $414 \pm 126$  versus  $408 \pm 66$  (SD) sec).<sup>28</sup> This is also a reason why heparin was not administrated in the control group. Second, heparin has been reported to increase the bioavailability of nitric oxide by liberating vessel-immobilized myeloperoxidase.<sup>6</sup> Thus, we expected that the beneficial effect of WBPA on endothelial function would be potentiated by heparin pretreatment.

It is tempting to compare the effect of heparin WBPA treatment with other therapeutic

modalities. In this study, the treadmill exercise time to 0.1 mV ST depression was significantly increased from  $261 \pm 123$  to  $400 \pm 164$  (SD) sec, which was comparable with the effect of heparin exercise treatment.<sup>13</sup> In angina patients enrolled in the multicenter study of enhanced external counterpulsation (MUST-EECP), the exercise time to 0.1 mV ST depression was increased significantly from  $337 \pm 18$  to  $379 \pm 18$  (SEM) sec.<sup>29</sup> Six week treatment (diltiazem, 360 mg/day) for patients with effort angina significantly increased the exercise time to 0.1 mV ST depression from  $198 \pm 24$  to  $324 \pm 36$  (SEM) sec.<sup>30</sup> Although direct comparison among these studies may be limited because of the differences in the patient population, medications and protocols in the treadmill exercise test, heparin WBPA treatment appears to be a promising therapeutic modality.

One limitation of the present study is the lack of a group of patients with WBPA without heparin. Since the present study was designed to document the efficacy of a new therapeutic modality for angina patients who are not indicated for percutaneous coronary intervention and/or coronary artery bypass grafting, we expected maximal effects of the treatment by combining WBPA with heparin. In future studies, it should be examined whether WBPA alone is also efficacious for relieving effort angina and improving LV dysfunction. Further investigations are needed to elucidate more precise mechanisms underlying the efficacy of the treatment. Prospective, randomized trials comprised of a large number of patients are also needed to confirm the effectiveness of this treatment.

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## Figure legends

**Figure 1.** Myocardial scintigrams in representative cases. Changes in myocardial perfusion scintigrams during adenosine infusion in representative cases (**A**), and changes in myocardial perfusion scintigrams at rest in the same representative cases as in A (**B**). Upper panels, short axial images; lower panels, horizontal long-axial images.

**Figure 2.** Summary data on myocardial scintigrams. Changes in summed stress score in myocardial scintigrams during adenosine infusion (**A**), and changes in summed rest score in myocardial scintigrams at rest (**B**). Bars indicate the mean  $\pm$  SD.

**Figure 3.** Summary data on global LV function. Changes in the LVEDVI index (**A**), LVESVI (**B**) and LVEF (**C**). Bars indicate the mean  $\pm$  SD. LV = left ventricular; LVEDVI = left ventricular end-diastolic volume index; LVEF = left ventricular ejection fraction; LVESVI = left ventricular end-systolic volume index.

**Table 1 Baseline patient characteristics**

Variable	Sedentary group (n = 13)	WBPA group (n = 13)
Age (years)	66 ± 10	69 ± 10
Men/women	10/3	9/4
Hypertension	10 (77%)	10 (77%)
Diabetes mellitus	7 (54%)	7 (54%)
Hypercholesterolemia	10 (77%)	8 (62%)
Cigarette smoker	6 (46%)	4 (31%)
Body mass index (kg/m <sup>2</sup> )	22.6 ± 3.4	23.5 ± 3.1
Renal failure	5 (38%)	5 (38%)
Number of involved coronary arteries	2.3 ± 0.8	2.5 ± 0.7
Ischemia-related coronary artery		
Right	4 (31%)	3 (23%)
Left anterior descending	7 (54%)	8 (62%)
Left circumflex	2 (15%)	2 (15%)
Healed myocardial infarction	5 (38%)	7 (54%)
Prior percutaneous coronary intervention	6 (46%)	6 (46%)
Prior coronary artery bypass grafting	5 (38%)	5 (38%)
Arteriosclerosis obliterans	1 (8%)	4 (31%)
Prior cerebral infarction	3 (23%)	0 (0%)
Canadian Cardiovascular Society of classification of effort angina		
Class II	11 (85%)	10 (77%)
Class III	2 (15%)	3 (23%)
Class IV	0 (0%)	0 (0%)
Medication		
Aspirin	13 (100%)	13 (100%)
Angiotensin converting enzyme inhibitor	3 (23%)	1 (8%)
Angiotensin II receptor blocker	6 (46%)	7 (54%)
Beta-blocker	8 (62%)	10 (77%)
Calcium-blocker	5 (38%)	6 (46%)
Statin	10 (77%)	6 (46%)
Pioglitazone	0 (0%)	1 (8%)
Diuretic	5 (38%)	6 (46%)

Values are the mean ± SD.

Sedentary group, patients with conventional medical therapy alone; WBPA group, patients with whole-body periodic acceleration therapy with heparin pretreatment plus conventional medical therapy.

**Table 2 Changes in treadmill exercise time and hemodynamic parameters at rest and 0.1 mV ST depression**

Variable	Sedentary group		WBPA group	
	Baseline	After treatment	Baseline	After treatment
Exercise time (sec)	269 ± 186	244 ± 159	261 ± 123	400 ± 164*†
Heart rate (beats/min)				
resting	70 ± 8	69 ± 9	68 ± 6	68 ± 8
ischemia	111 ± 15	107 ± 17	112 ± 10	115 ± 9
Systolic blood pressure (mmHg)				
resting	122 ± 12	125 ± 11	121 ± 12	119 ± 12
ischemia	138 ± 19	134 ± 21	136 ± 24	163 ± 29*†
Rate-pressure product × 10 <sup>-2</sup> (mmHg × beats/min)				
resting	86 ± 15	86 ± 14	82 ± 10	81 ± 10
ischemia	154 ± 37	145 ± 41	154 ± 35	189 ± 39*†

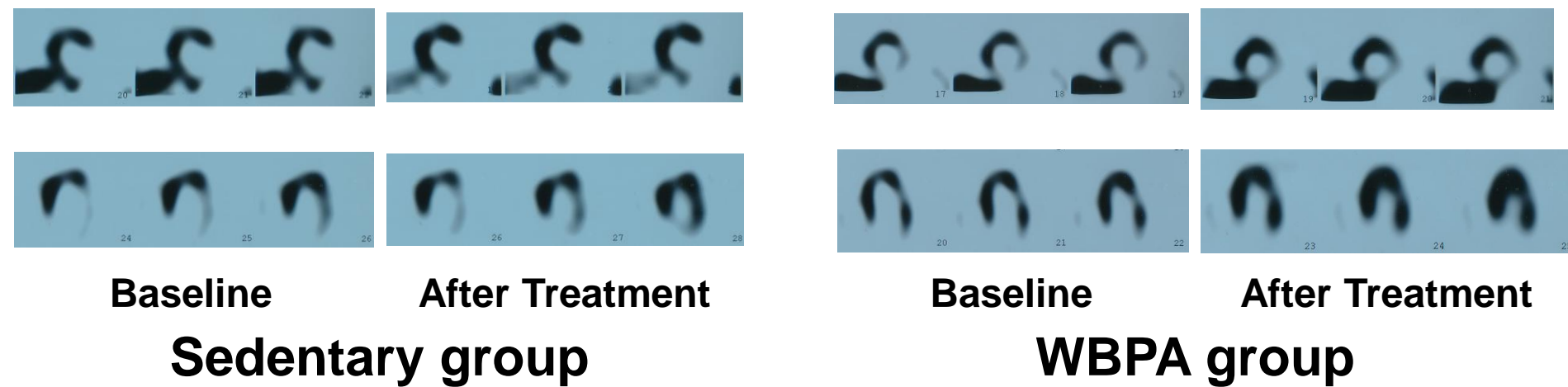
Data are presented as the mean value ± SD.

Sedentary group, patients with conventional medical therapy alone; WBPA group, patients with whole-body periodic acceleration therapy with heparin pretreatment plus conventional medical therapy. \*p < 0.01 vs. baseline values; †p < 0.01 vs. Sedentary group.

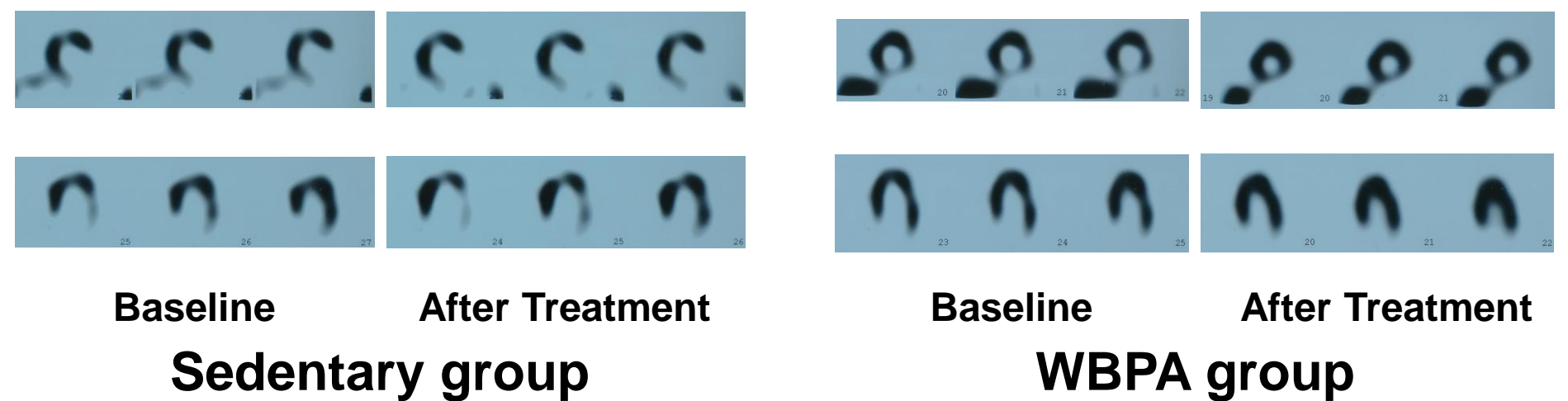
WBPA = whole-body periodic acceleration.

# Figure 1

## A During Adenosine Infusion

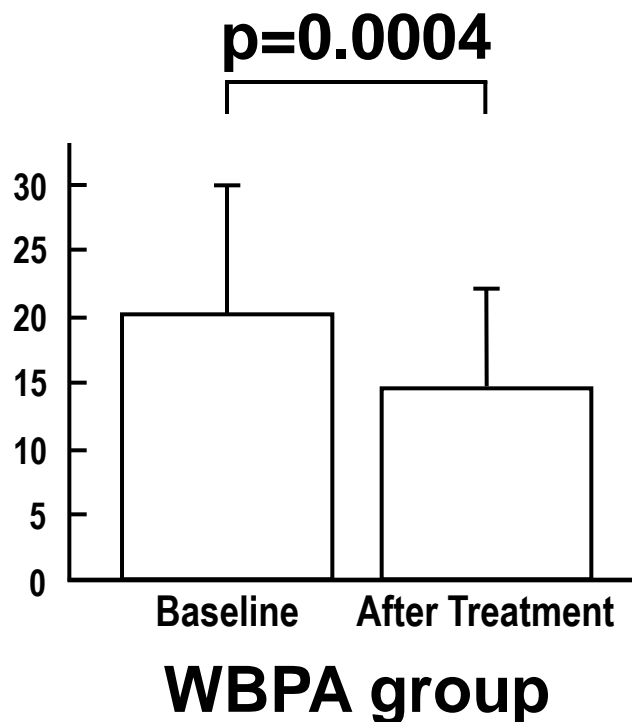
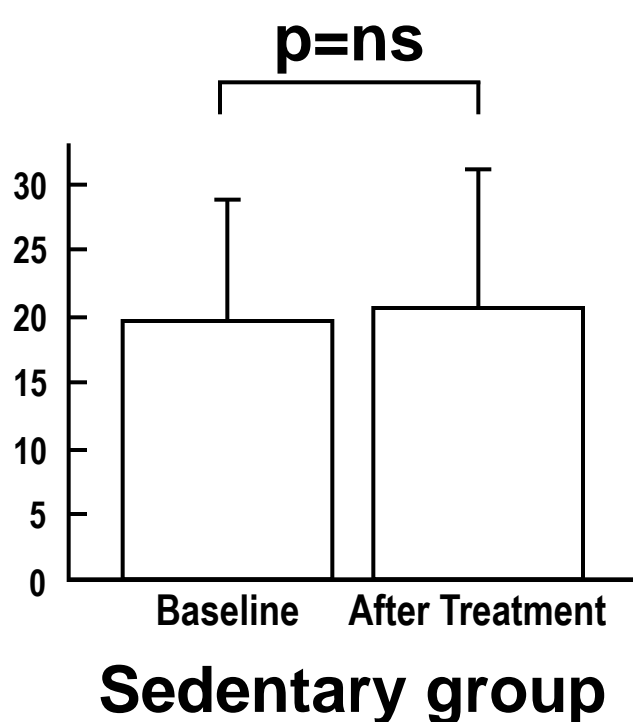


## B At rest

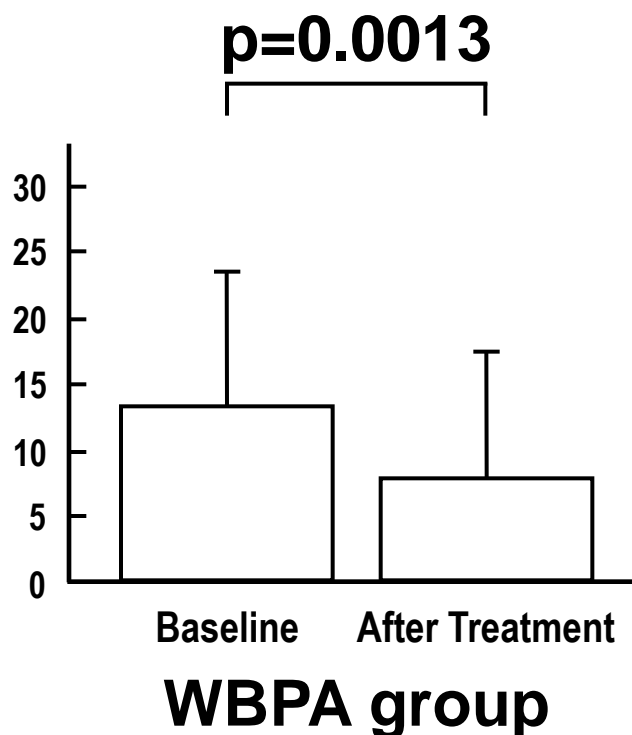
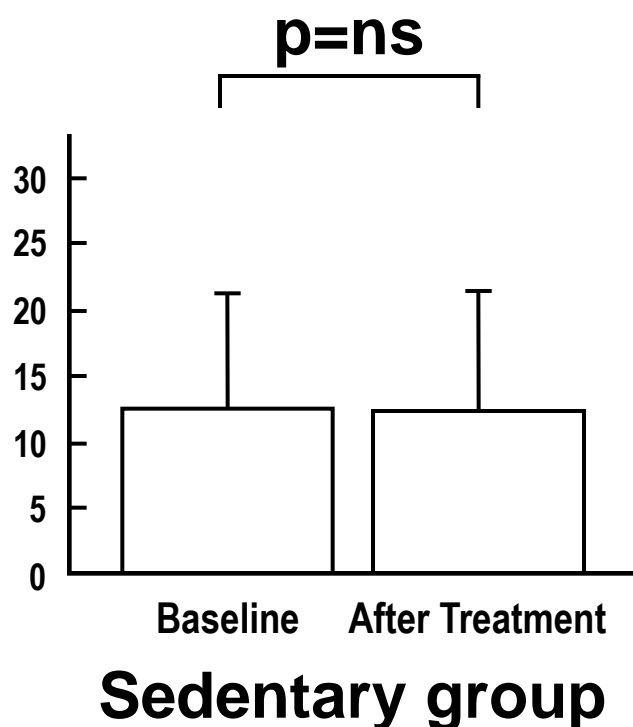


# Figure 2

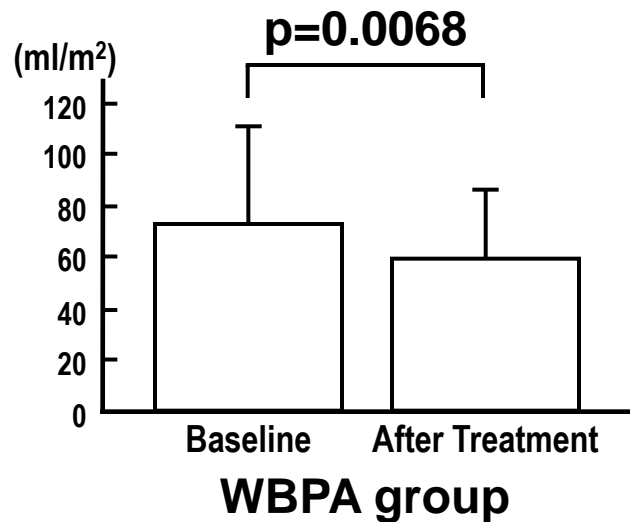
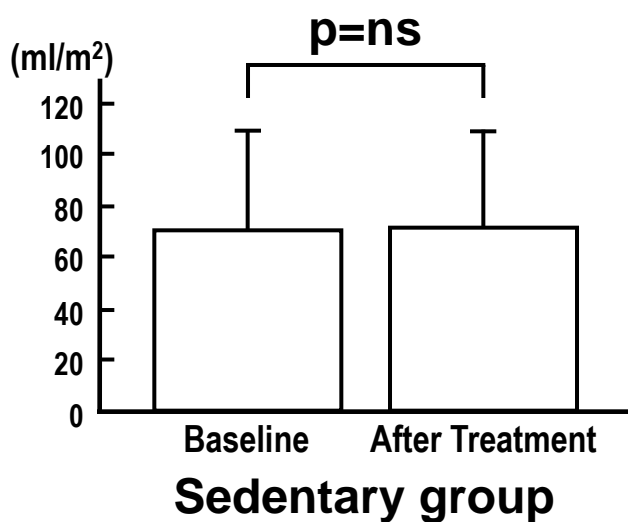
## A Summed Stress Score



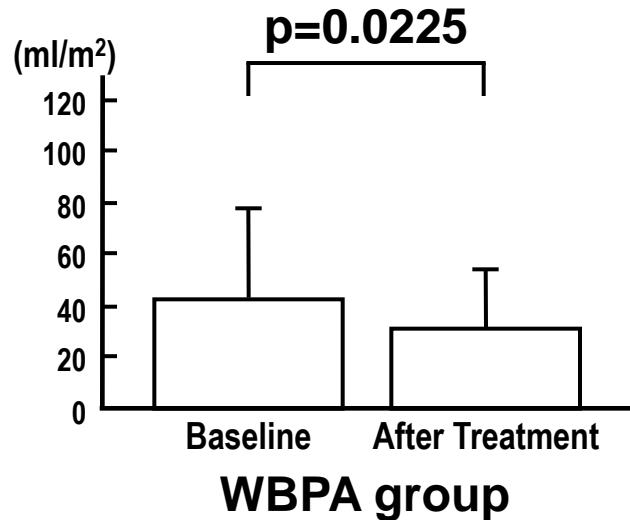
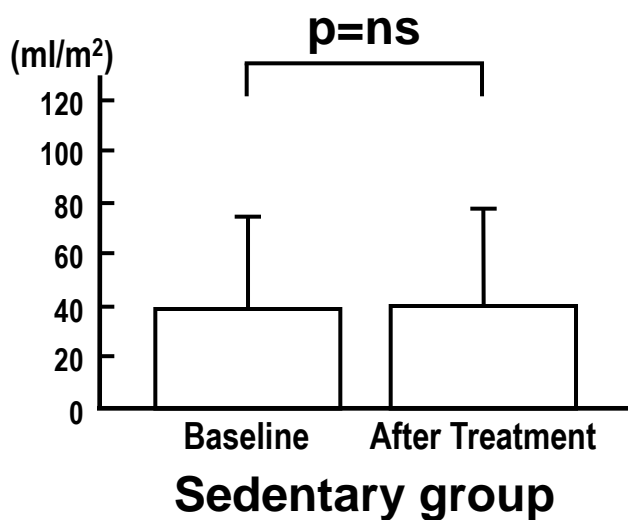
## B Summed Rest Score



## A LVEDVI



## B LVESVI



## C LVEF

